

REMARKS

Claims 1-36 were pending in the application. Claims 1, 2, 4, and 30-34 are hereby cancelled without prejudice to pursuing the cancelled claims in this or other continuing applications. Claims 3, 5, 7, 8, 9, 10, 22, 23, 25, and 27 have been amended. Upon entry of these amendments, Claims 3, 5-29, and 35-36 will be pending and under active consideration. Claims 3, 5, and 10 are independent. The specification is amended to correct informalities as required by the Examiner. The amendments are supported fully by the claims and/or specification as originally filed and, thus, do not represent new subject matter.

Without acquiescing in the rejections set forth against them, Claims 1, 2, 4, and 30-34 are cancelled herein without prejudice to pursuing the cancelled subject matter in this or other continuing or divisional applications. These claims are cancelled solely to advance the prosecution of the present application.

Claims 5, 10, 22, 23, 25, and 27 have been amended to point out more particularly and claim more distinctly that which Applicant regards as her invention. The afore-mentioned claims are amended to clarify their language as required by the Examiner.

Claims 3 and 5 are amended to incorporate the limitations of cancelled Claim 1. The amendments are supported fully by the claims and/or specification as originally filed and, thus, do not represent new subject matter. Claims 3 and 5 are both now independent. Claims 7, 8, and 9 are amended to change their dependency from cancelled Claim 1 to now independent Claim 3.

Applicant respectfully requests entry of the amendments and remarks made herein into the file history of the present invention. Reconsideration and withdrawal of the rejections set forth in the above-identified Office Action are respectfully requested.

I. The Rejections Under 35 U.S.C. § 102(e) Should Be Withdrawn

The Office Action, at paragraph 27, rejects Claims 1, 2, 4, 7, and 9 as allegedly being anticipated by U.S. Patent No. 6,355,431 to Chee *et al.* (hereinafter, "Chee"), under 35 U.S.C. § 102(e), for the reasons of record. Applicant traverses respectfully.

Without acquiescing in the propriety of the rejections, without prejudice to pursuing the cancelled subject matter in this or other applications, and solely to advance prosecution of the present application, Applicant cancels Claims 1, 2, and 4 by the amendments herein. Claims 3 and 5 are amended to incorporate the limitations of cancelled Claim 1, and are both now independent. Claims 7, 8, and 9 are amended to change their dependency from cancelled Claim 1 to now independent Claim 3. Accordingly, Applicant submits respectfully that the rejections to Claims 1, 2, 4, 7, and 9 under 35 U.S.C. § 102(e) have been rendered moot, and Applicant requests respectfully that the rejections to Claims 1, 2, 4, 7, and 9 under 35 U.S.C. § 102(e) be withdrawn.

II. The Rejections Under 35 U.S.C. § 103(a) Should Be Withdrawn

The Office Action, at paragraph 29, rejects Claims 30-34 as allegedly being obvious over Chee under 35 U.S.C. § 103(a) for the reasons of record. Applicant traverses respectfully.

Without acquiescing in the propriety of the rejections, without prejudice to pursuing the cancelled subject matter in this or other applications, and solely to advance prosecution of the present application, Applicant cancels Claims 30-34 by the amendments

herein. Accordingly, Applicant submits respectfully that the rejection of Claims 30-34 under 35 U.S.C. § 103(a) have been rendered moot, and Applicant requests respectfully that the rejection of Claims 30-34 under 35 U.S.C. § 103(a) be withdrawn.

III. Rejections Under 35 U.S.C. § 112, Second Paragraph

At paragraphs 4-25 of the Office Action, Claims 1-36 are rejected variously under 35 U.S.C. § 112, second paragraph, as allegedly being vague and indefinite for failing to point out particularly and claim distinctly the subject matter regarded as the invention. Applicant traverses respectfully.

At paragraph 5 of the Office Action, Claim 1 is rejected as allegedly being vague and indefinite in view of the phrase “at least one of detecting the presence of the spectrally addressable ligated products or analyzing the nucleic acid sequence of the spectrally-addressable ligated products” because it is allegedly unclear what it intended. The Office Action suggests that the phrase “at least one” needs to be deleted in order to understand the claim. Applicant traverses respectfully.

While Claim 1 is cancelled without prejudice by the amendments made herein, and the rejection of Claim 1 under 35 U.S.C. § 112, second paragraph, has been rendered moot thereby, the limitations of Claim 1 have been added into Claims 3 and 5. Accordingly, Applicant will present arguments in support of the language of Claim 1 as applicable to Claims 3 and 5. Applicant submits respectfully that the intention of the cited language is indeed clear. The method of the present invention as claimed in Claim 1, now Claims 3 and 5, may include *either one or both* of the steps of detecting the presence of the spectrally addressable ligated products or

analyzing the nucleic acid sequence of the spectrally-addressable ligated products. The phrase “at least one of” denotes that, at a minimum, one of the elements recited after the phrase must be included and that, at a maximum, all of the elements may be included. Hence, Applicant submits respectfully that the language “at least one of” preceding the recitation of “detecting the presence of the spectrally addressable ligated products or analyzing the nucleic acid sequence of the spectrally-addressable ligated products” clearly delineates the metes and bounds of the scope of the invention as claimed in Claim 1, now Claims 3 and 5.

At paragraph 6, the Office Action rejects Claim 5 as allegedly vague and indefinite in view of the phrase “the sample is contacted with two subsets of free probes and one subset of spectrally-addressable bound probes, wherein the first subset of free probes is specific for the first portion of the one or more first target nucleic acid sequences and the second set of spectrally-addressable bound probes is specific for the first portion of the one or more second target nucleic acid sequences” because it is unclear what it intended. Applicant traverses respectfully.

Without acquiescing in the propriety of the rejection, Applicant amends Claim 5 herein to recite “second set of free probes” in place of “second set of spectrally-addressable bound probes.” In view of the amendment, Applicant submits respectfully that the meaning of Claim 5, as amended, is clear and definite.

At paragraph 7, the Office Action rejects Claim 8 as allegedly vague and indefinite because it is allegedly unclear how the relative amount of fluorescence dye incorporated into the spectrally-addressable bound probes can be used to distinguish different bound probes. The Office Action further notes that, since a substantially same amount of fluorescent dye is

incorporated into each bound probe, the relative amount of fluorescence dye incorporated into the spectrally-addressable bound probes must be the same. Applicant traverses respectfully.

Respectfully, Applicant draws Examiner's attention to the *complete* text of Claim 8, which recites, notably, that "a substantially same amount of fluorescent dye is incorporated into each bound probe *of a subset*," and that "one *subset* of spectrally-addressable bound probes is distinguishable from another *subset*" of such probes on the basis of the fluorescent dyes incorporated into the particles of each subset (emphasis added). Applicant submits respectfully that the language of the claim includes within its scope the condition in which the various subsets of spectrally-addressable bound probes incorporate different amounts of dye (although each bead within each subset has substantially the same amount of the dye as each other bead of the same subset) and are, thus, distinguishable one from another based on that differing amount of dye. Hence, Applicant submits respectfully that the invention as claimed in Claim 8 is clearly defined.

At paragraph 8, the Office Action rejects Claim 10 as allegedly vague and indefinite in view of the phrases "at least one subset of microspheres to which are coupled bound probes" and "coupling a bound probe to a microsphere," which allegedly construe a probe blocked by particles at both the 3' and 5' ends since Applicant has allegedly defined a bound probe as a probe that is coupled to a solid support (*e.g.*, a microsphere). Applicant traverses respectfully.

Without acquiescing in the propriety of the rejection, Applicant amends Claim 10 herein as noted above to clarify the intended meaning of the claim, that the microspheres to which the bound probes are coupled *are* the solid support which is comprised within a bound probe as previously defined. In view of the amendment, Applicant submits respectfully that the meaning of Claim 10, as amended, is clear and definite.

At paragraph 9, the Office Action rejects Claim 10 as allegedly vague and indefinite in view of the phrase “the bound probes of a given subset of microspheres” because microspheres allegedly do not include bound probes. Applicant traverses respectfully. As noted above, Claim 10 is amended herein and is clear as to the relationship between bound probes and microspheres as claimed in Claim 10. As claimed in Claim 10, bound probes comprise microspheres, and Claim 10 now recites “microspheres of a given subset of bound probes,” which recitation is an accurate reflection of a definition of bound probes according to the specification as filed and consistent with the intention of Claim 10, as filed. Hence, Applicant submits respectfully that the invention as claimed in Claim 10, as amended, is clearly defined.

At paragraph 10, the Office Action rejects Claims 13 and 14 as allegedly vague and indefinite because it is allegedly unclear what it intended by the expression “the free probe further comprising a phosphate at the other of their end.” The Office Action argues that, since the bases in a nucleic acid probe are connected by phosphodiester bonds, both ends of a nucleic acid contain phosphates. Applicant traverses respectfully.

While Applicant acknowledges that the bases in a nucleic acid probe are connected by phosphodiester bonds, Applicant respectfully points out that phosphodiester bonds exist *between* bases of a polynucleotide and, hence, do not reflect the condition of the *ends* of the polynucleotide. Applicant points out respectfully that, while naturally occurring polynucleotides often include 5' phosphate moieties, it is not the case that all polynucleotides necessarily have such phosphate end groups. In fact, Applicant points out respectfully that one skilled in the art is well aware that many polynucleotides, particularly those that are synthesized artificially for use as nucleic acid probes, do not contain terminal phosphate groups and must be “kinased”

(phosphorylated by the action of a kinase enzyme) before ligation with a ligase enzyme is possible. Thus, Applicant submits respectfully that Claims 13 and 14 as filed are clear and definite in their intent and meaning.

At paragraph 11, the Office Action rejects Claim 16 as allegedly vague and indefinite in view of the phrases “the bound probes differ in that the nucleotide found at one end of one subset differs from that found at the corresponding end of the other subset” and “wherein the nucleotide sequences comprising the at least two subsets of bound probes are otherwise substantially identical.” The Office Action alleges that these phrases are unclear as to their meaning. Applicant traverses respectfully.

As noted previously, and as claimed in Claim 10, free probes and bound probes comprise an oligonucleotide having a predetermined sequence of nucleic acids. Claim 16 adds the limitation that the nucleic acid sequences amongst the various subsets of free probes and bound probes are substantially identical, with the exception that the nucleotide found at one end of the bound probes, and at the corresponding end of the free probes, is different amongst the various subsets. Thus, Applicant submits respectfully that the meaning of Claim 16 as filed is clear and definite.

At paragraph 12, the Office Action rejects Claim 20 as allegedly vague and indefinite because it is unclear what it intended. The phrase “the nucleotide and the detectable label found at opposite ends of one set differing from that nucleotide and the detectable label found in the corresponding ends of the other set” is allegedly unclear because it is unclear whether the free probes have one detectable label or two detectable labels. Applicant traverses respectfully.

Claim 20 provides that the assay of the present invention includes at least two sets of free probes. Each probe in each set of free probes comprises a nucleotide sequence having two opposite ends. At one end is a detectable label. At the other, opposite, end is a single nucleotide. The probe ends having the single nucleotide of one set correspond to the probe ends having the single nucleotide in another set. Likewise, the ends with the detectable label of one set correspond to the ends having the detectable label in another set. Apart from these two features, the nucleotide sequence of all of the probes amongst the various sets is substantially identical. Within each set of probes the detectable labels are the same and the single end nucleotides are the same. However, amongst the various sets, the single end nucleotide are different and the detectable labels are different, thus providing the differences that distinguish each individual set. Applicant submits respectfully that the language of Claim 20 clearly and unambiguously states this meaning, and Applicant submits respectfully that the language of Claim 20 is clear and definite as filed.

Claim 20 was also rejected, at paragraph 13 of the Office Action, as allegedly vague and indefinite because it is unclear what it intended by the phrase “wherein the nucleotide sequences comprising the at least two sets of free probes are otherwise substantially identical.” The Office Action alleges that the phrase is unclear because it is difficult to understand how the nucleotide sequences comprising the at least two sets of free probes can be considered to be substantially identical if nucleotide sequences and detectable labels in two sets of free probes are different in one end of the probes. Applicant traverses respectfully.

As noted above, the nucleotide sequences of probes amongst the various sets is substantially identical with the exception of the single end nucleotide and detectable label at

corresponding opposite ends of the probes of the various sets. This exception is clearly stated in the language of Claim 20 by the term “otherwise substantially identical.” Applicant submits respectfully that this language of Claim 20 is clear and definite as filed.

At paragraph 14, the Office Action rejects Claim 22 as allegedly vague and indefinite because it is unclear what it intended by the phrase “the oligonucleotides of the at least one set of free probes and at least one subset of microsphere have 5’ and 3’ ends.” This phrase is allegedly unclear because the microsphere, itself, can not include an oligonucleotide and does not have 5’ and 3’ ends. Applicant traverses respectfully. Without acquiescing in the propriety of the rejection, Applicant amends Claim 22 herein to replace the term “microsphere” with the term “bound probe.” As bound probes have 3’ and 5’ ends, Applicant submits respectfully that the language of Claim 22, as amended, is clear and definite.

At paragraph 15, the Office Action rejects Claim 22 as allegedly vague and indefinite because it is unclear what it intended by the phrase “the free probes of a given set include a phosphate at their 5’ end.” The Office Action alleges that, since the bases in a nucleic acid probe are connected by phosphodiester bonds and both ends of a nucleic acid contain phosphates, it is unclear which phosphate can be considered as a phosphate at their 5’ end. Applicant traverses respectfully.

As noted above, Applicant submits respectfully that the Office Action errs in asserting that both ends of a nucleic acid contain phosphates. A phosphodiester bond is formed by the action of a ligase upon the 5’ phosphate at one oligonucleotide end and the 3’ hydroxyl group at another oligonucleotide end. Thus, if there is a phosphate group on an oligonucleotide at all, there is only a phosphate group at one end, the 5’ end. Furthermore, even if there were,

hypothetically, a phosphate group at the 3' end as well as the 5' end, there would be no confusion as to which phosphate was the one at the 5' end, as the oligonucleotide has, inherently, a clearly defined 3' and 5' end apart from the presence of the phosphate group. The 3' and 5' ends are not defined by the presence of the phosphate group, but rather by the position within the ribose ring structure of the carbon atom to which the phosphate (or other group) is attached. Thus, Claim 22, as amended, is clear and definite as to its meaning.

At paragraph 16, the Office Action further rejects Claim 22 as allegedly vague and indefinite because it is unclear what it intended by the phrase "the modifier moiety is an amine which couples the 5' end of the oligonucleotide of the bound probe to a carboxylic acid group on the microsphere." Furthermore, the Office Action alleges that Figures 1 and 6 teach no such bound probe. Applicant traverses respectfully.

Applicant submits respectfully that, as defined in Claim 10, from which Claim 22 depends, oligonucleotides of bound probes comprise a modifier moiety at *one end*. Claim 22 provides the limitation that the modifier moiety is an amine group at the 5' end of the bound probe. This amine group is used to couple, covalently, the 5' end of the probe to a carboxylic acid group on the microsphere. Thus, Applicant submits respectfully that the bound probe of the claimed invention has a microsphere at only one end, the 5' end of the bound oligonucleotide, and the 3' end is free to participate in a ligation reaction with the 5' phosphate of a free probe. Furthermore, both Figures 1 and 6, particularly Figure 6 at bound probes labeled ASP1 and ASP2, show bound probes comprised of an oligonucleotide bound at its 5' end to a microsphere and having a free 3' end. Figure 6 shows further a free probe, labeled P3, that has a phosphate group at its 5' end which may participate in the formation of a phosphodiester bond with the free

3' end of one of the bound probes. Thus, Applicant submits that the language of Claim 22, as amended, is clear and definite in its meaning.

Claim 23 is rejected, at paragraphs 17-19 of the Office Action, as allegedly vague and indefinite because it is unclear what it intended. The Office Action alleges that the 5' and 3' ends of the bound probe in the claim appear to have attached particles, that the meaning of the phrase "a portion of the oligonucleotide at the 3' end of one subset differs from the a portion of the oligonucleotide at the 3' end of the other subset" is unclear, and that the phrase "wherein the nucleotide sequences comprising the at least two sets of bound probes are otherwise substantially identical" is unclear. Applicant traverses respectfully.

The claimed invention comprises at least two subsets of microsphere-bound oligonucleotide probes, termed "bound probes." The bound probes each comprise an oligonucleotide sequence having two opposite ends. At one end is attached the microsphere. At the other end, the at least the one terminal nucleotide, and in some cases the terminal group of nucleotides, is termed a "portion" of the oligonucleotide. Within each subset, the sequence of the terminal "portion" of the oligonucleotide is the same, and the microsphere at the other, opposite, end is the same. Amongst the various sets, however, these terminal "portions" are different (having different nucleotide sequence) and the microspheres are different (having a unique spectral address), thus providing the discriminating features that define each subset. Apart from the differences in the microsphere and terminal "portion," the oligonucleotide sequence of the probes of all subsets is substantially identical. Without acquiescing in the propriety of the rejection, Claim 23 is amended herein to make its meaning more clear and definite.

At paragraph 20, the Office Action rejects Claim 24 as allegedly vague and indefinite because it is allegedly unclear what it intended by the phrase “wherein the nucleotide sequences comprising the at least two sets of free probes are otherwise substantially identical.” The Office Action alleges that it is difficult to understand how the nucleotide sequences comprising the at least two sets of free probes can be considered to be substantially identical when, as shown in the claim, a portion of the 5’ end of the probes is different. Applicant traverses respectfully.

As noted above, the term “otherwise” prior to “substantially identical” makes clear to one skilled in the art that, other than a portion of the 5’ end which differs between members of different sets, the nucleotide sequences of the oligonucleotides comprising the free probes are substantially identical. Applicant submits respectfully that the meaning of Claim 23 is clear and definite as filed.

The Office Action, at paragraph 21, rejects Claim 25 as allegedly vague and indefinite in view of the phrase “substantially the same reaction vessel” because it is allegedly unclear that this phrase mean the same reaction vessel or different reaction vessels. Applicant traverses respectfully. Without acquiescing in the propriety of the rejection, Applicant amends Claim 25 herein to recite “carried out in a single reaction vessel.” Applicant submits respectfully that Claim 25, as amended, is clear and definite.

At paragraph 22, the Office Action rejects Claim 27 as allegedly vague and indefinite because it is allegedly unclear what it intended. The Office Action alleges that the concentration of a fluorescent dye on the microspheres can not be used to distinguish fluorescence-labeled microspheres since concentration means amount per unit. Applicant traverses respectfully. Without acquiescing in the propriety of the rejection, Applicant amends Claim 27 herein to recite

“microspheres of the one subset harbor at least one fluorescent dye that emits, upon exposure to an excitatory stimulus, a signal having an intensity that differs from the intensity of a signal emitted by the at least one fluorescent dye harbored by the microspheres of the other subset.” Applicant submits that Claim 27, as amended, is clear and definite.

At paragraph 23, Claim 27 is rejected by the Office action as allegedly vague and indefinite in view of the phrase “the microspheres of one subset can be distinguished from the microspheres of the other subset” because the word “can” in the phrase represents an ability of the microspheres. Thus, the Office Action alleges that Claim 27 cannot be considered as a method step. Applicant traverses respectfully. Applicant submits respectfully that the limitation of Claim 27 is not intended as a method step, but rather as a limitation of one of the components of the assay method of the claimed invention. Therefore, Applicant submits respectfully that the language of Claim 27 is clear and definite.

At paragraph 24, Claim 28 is rejected by the Office action as allegedly vague and indefinite in view of the phrase “the spectrally addressable microspheres of one subset can be distinguished from the spectrally addressable microspheres of another subset” because the word “can” in the phrase represents an ability of the microspheres. Thus, the Office Action alleges that Claim 28 can not be considered as a method step. Applicant traverses respectfully. Applicant submits respectfully that the limitation of Claim 28 is not intended as a method step, but rather as a limitation of one of the components of the assay method of the claimed invention. Therefore, Applicant submits respectfully that the language of Claim 28 is clear and definite.

At paragraph 25, the Office Action rejects Claim 30 as allegedly vague and indefinite because it is allegedly unclear how to interpret the phrase “bound probes coupled to spectrally

addressable microspheres.” Applicant traverses respectfully. Without acquiescing in the propriety of the rejection, and without prejudice, Applicant cancels Claim 30 by the amendments herein. Therefore, Applicant submits respectfully that the rejection of Claim 30 has been rendered moot.

On the basis of the foregoing, Applicant submits respectfully that the 35 U.S.C. § 112, second paragraph, rejections of Claims 1-36 have been overcome, and Applicant requests respectfully that the 35 U.S.C. § 112, second paragraph, rejections of Claims 1-36 be withdrawn.

IV. The Objection To The Specification Should Be Withdrawn.

At paragraph 2, the Office Action objects to the specification because of alleged informalities related to the absence of SEQ ID numbers and the presence of typographical errors throughout the specification. Applicant traverses respectfully.

Applicant respectfully directs Examiner’s attention to Exhibit B of the Amendment, which contains a substitute specification under 37 C.F.R. § 1.121(b). Applicant avers that the substitute specification contains no new matter. Applicant submits respectfully that the substitute specification corrects the afore-mentioned informalities; in particular, the description of FIG. 6 has been amended to recite that the first PCR primer is “S” and the biotin reporter is “R” as indicated on the drawing, and to insert SEQ ID numbers. Accordingly, Applicant requests respectfully that the objection to the specification be withdrawn.

CONCLUSION

Applicant submits that the application is in condition for allowance. Favorable reconsideration, withdrawal of the rejections set forth in the above-noted Office Action, and an early Notice of Allowance are requested.

Applicant's undersigned attorney may be reached in our Washington, D.C. office by telephone at (202) 625-3500. All correspondence should be directed to our address given below.

AUTHORIZATION

Applicant believes there is no fee due in connection with this filing. However, to the extent required, the Commissioner is hereby authorized to charge any fees due in connection with this filing to Deposit Account 50-1710 or credit any overpayment to same.

Respectfully submitted,



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